Usefulness of a Coronary Artery Disease Predictive Algorithm to Predict Global Risk for Cardiovascular Disease and Acute Coronary Syndrome

Masood Younus, MD[a], Wenjun Fan, MD, MS[a], Douglas S. Harrington, MD[b,c,1], and Nathan D. Wong, PhD[a,1,*]

Traditional global risk assessment for cardiovascular disease fails to identify a significant percentage of the population initially classified at low or intermediate risk of cardiovascular disease that are actually at high risk for acute coronary syndrome (ACS). We examined a coronary artery disease predictive algorithm (CADPA) that includes 9 biomarkers involved in the pathogenesis of atherosclerosis initiated by endothelial damage and repair (hepatocyte growth factor, soluble FAS, Fas ligand, eotaxin, cutaneous T cell-attracting chemokine, monocyte chemotactic protein-3, interleukin-16, hemoglobin A1c, high-density lipoprotein-cholesterol), in addition to age, gender, diabetes, and family history of myocardial infarction that more accurately predicts 5-year risk of ACS to identify the patient population at discordantly high risk. We found that 34% of patients at low risk by global risk assessment and 72% of patients at intermediate risk by global risk assessment were actually at discordantly high risk for ACS. This patient population was disproportionately male and older in age. The biomarkers (per standard deviation) that most predicted the odds (95% confidence levels) of discordance were interleukin-16 (2.59 [2.21 to 3.03]), Fas Ligand (0.50 [0.43 to 0.57]), hepatocyte growth factor (1.72 [1.50 to 1.98]), soluble FAS (2.19 [1.86 to 2.58]), cutaneous T cell-attracting chemokine (0.46 [0.40 to 0.53]), and eotaxin (1.78 [1.56 to 2.03]), in addition to age, HbA1c, low-density lipoprotein-cholesterol, and glycated hemoglobin. In conclusion, although future prospective study validation is needed to establish a causal relation between CADPA and cardiovascular events, our study defines a patient population considered low to intermediate risk by conventional clinical evaluation, but who is at discordantly high risk indicated by the endothelial injury serum biomarker algorithm CADPA and may benefit from further evaluation and medical management. **© 2018 Elsevier Inc. All rights reserved.** **(Am J Cardiol 2019;123:769−775)**

Atherosclerotic cardiovascular disease has significant morbidity and mortality. Previous studies have shown both prevalence and risk assessment of coronary events to be underestimated.[1−3] Despite recent advancements, recognizing patients with subclinical disease at high risk for experiencing a coronary event is a challenge due to its inherently unpredictable nature.[4] Additionally, studies suggest that the risk of plaque disruption that results in acute coronary syndromes (ACS) depends more on plaque composition than degree of stenosis.[5] We examined in this study whether a novel multibiomarker based coronary artery disease predictive algorithm (CADPA) that measures endothelial damage would identify persons at high risk for ACS that were identified at low to intermediate risk based on global risk assessment.

Methods

A total of 6,298 patients (aged 23 to 104, 43% women) without known cardiovascular disease were selected from a clinical registry of patients seen by multiple physician specialties throughout the United States. The patients filled out a study questionnaire to collect data on current hypertension and lipid-lowering medications, family history of cardiovascular disease, smoking status, and the presence of significant stress in their lives. A single blood pressure measurement was taken using a manual blood pressure cuff in the clinic. Blood was drawn to measure routine fasting cardiovascular labs, including hemoglobin A1c, lipid panel, and the biomarkers used for CADPA, discussed below. Other blood markers were also measured including apolipoprotein A1, apolipoprotein B, lipoprotein a, high sensitivity C-reactive protein, which are not part of the CADPA test. Using these data, a global 5-year cardiovascular risk by modified Framingham risk (mFR) assessment and the CADPA 5-year risk of ACS were measured.[6]

The CADPA risk assessment tool (GD Biosciences, Irvine, California) was developed using gene expression studies that

[a]Heart Disease Prevention Program, Division of Cardiology University of California, Irvine School of Medicine, Irvine, California; [b]GD Biosciences, Irvine, California; and [c]USC School of Medicine, Los Angeles, California. Manuscript received September 5, 2018; revised manuscript received and accepted November 28, 2018.

Abbreviations: CADPA, coronary artery disease prediction algorithm; ACS, acute coronary syndrome.

[1]Drs. Harrington and Wong served as cosenior investigators.

See page 774 for disclosure information.

*Corresponding author: Tel: +019498245433; fax: +019498245561.

E-mail address: ndwong@uci.edu (N.D. Wong).

0002-9149/© 2018 Elsevier Inc. All rights reserved.
https://doi.org/10.1016/j.amjcard.2018.11.044

Table 1
List of biomarkers and their physiologic function in cardiac lesions

Biomarker	Relation to endothelial damage and unstable cardiac lesions
Measures formation	
Cutaneous T cell-attracting chemokine	Recruits T-cells to the injured site (modulates repair and inflammation)
Eotaxin	Recruits eosinophils to the site of injury (remove fibrin)
Interleukin-16	Initiates the repair and inflammation process (cell signaling)
Monocyte chemotactic protein-3	Recruits and activates macrophages to the site of injury (foam cells)
Measures progression	
Fas ligand	Prevents programmed cell death (apoptosis)
Hepatocyte growth factor	Tissue repair and angiogenesis
Soluble FAS	Initiates programmed cell death (apoptosis)
	Stimulates tissue and repair
Measures clinical risk factors	
High-density lipoprotein-cholesterol	Helps remove bad cholesterol and neutralizes free radicals
Hemoglobin A1c	Diabetes marker

These biomarkers reflect the underlying pathways of unstable cardiac lesion formation and progression. They are grouped by their role in measuring formation, measuring progression, or measuring clinical risk factors.

identified over 250 proteins from approximately 10 pathways expressed in mice with unstable coronary lesions. From these, 45 clinically measurable serum biomarkers that are also expressed in humans with coronary disease were selected by univariate analysis to predict ACS in a 5-year timeframe.[6,7] These unique biomarkers associated with endothelial injury and repair were tested together with currently available biomarkers, such as high sensitivity C-reactive protein and myeloperoxidase, as well as global risk factors such as age, gender, and blood pressure in various permutations, using a forward selection method. Optimum algorithm size was determined by 3 statistical systems including Akaike, Bayesian, and Drop-in Deviance methods. Fitting a weighted Cox proportional hazards model to all data and restricting the number of protein biomarkers yielded the final CADPA model that contained 4 clinical factors along with the 9 protein biomarkers: hepatocyte growth factor, soluble FAS, Fas ligand, eotaxin, cutaneous T cell-attracting chemokine, monocyte chemotactic protein-3, interleukin-16, high-density lipoprotein-cholesterol, and hemoglobin A1c. Additional information about these biomarkers is shown in Table 1. Four global risk factors (age, gender, diabetes, and family history of myocardial infarction) were also selected to be a part of the clinical algorithm to consistently predict ACS in 5 years. This biomarker algorithm was then validated by the National Heart, Lung, and Blood Institute in the Multiethnic Study of Atherosclerosis population. This process is described in further detail in Figure 1 and in a previous study.[6]

Of the 6,298 patients in the original data set, 3,539 were removed due to missing data. A total of 397 patients with outliers and extreme values were also omitted from the final cohort to maintain a bell-curve distribution, resulting in a final cohort of 2,362 patients. All variables were individually standardized. Patients were characterized into low (<3.5%), intermediate (3.5% to 7.49%), and high (≥7.5%) 5-year risk for ACS based on the patient's CADPA score. These patients were also subdivided into 3 categories based on low (<3.5%), intermediate (3.5% to 7.49%), and high (≥7.5%) of cardiovascular disease based on mFR. A subgroup of patients was identified who scored low or intermediate risk on mFR and high risk on CADPA defined the discordant group. Percentages of men versus women in the discordant group were compared between the 3 mFR risk groups.

Baseline characteristics including demographic, habits, medical history, and lab data were compared between CADPA risk categories with descriptive bivariate analysis using both the Chi-square test of proportions for categorical variables and analysis of variance for continuous variables. These same variables were again compared between the discordant and nondiscordant groups.

Stepwise logistic regression analysis was performed on the discordant group with the following continuous variables: eotaxin, interleukin-16, soluble FAS, high-density lipoprotein-cholesterol, monocyte chemotactic protein-3, cutaneous T cell-attracting chemokine, hemoglobin A1c, hepatocyte growth factor, Fas Ligand, age, apolioprotein A1, apolipoprotein B, body mass index, high-density lipoprotein-cholesterol, low density lipoprotein-cholesterol, lipoprotein (a), triglycerides, systolic blood pressure, diastolic blood pressure, and high sensitivity C-reactive protein. The following categorical variables were also entered into the model: taking blood pressure medication, taking lipid medication, diabetic status, family history of cardiovascular disease, gender, obesity, and currently smoking. The stepwise logistic function had an entry cutoff of p=0.15 and stay cutoff of p= 0.15. SAS 9.0 statistical software was used for all analyses.

There was greater than 80% power to detect differences in discordance of 10% or greater (e.g., 50% vs 60%), between risk groups with at least 400 subjects in each group (with an alpha 2-tailed of 0.05) showing our sample sizes in each risk group were sufficient to detect differences in discordance of at least 10%.

Results

The baseline characteristics of the study participants are shown in Table 2. Overall 74%, 21%, and 5% of participants were classified as low, intermediate, and high risk by the 5-year mFR global risk score. 29.3% were categorized as low 5-year risk for ACS by CADPA, 26.7% were intermediate risk, and 45% were high risk. A total of 43.7% of low risk patients, 54.3% of intermediate patients, and 67.0% of high risk patients were men. The mean ages of the 3 groups were 50.1, 61.0, and 69.8 years for low, intermediate, and high risk, respectively. The mean age of our population overall was 62 years, and 57% were men. Table 3 compares the baseline characteristics of the excluded patients with our final patient cohort. There were slight, although statistically significant differences in most risk factors between those included versus not included,

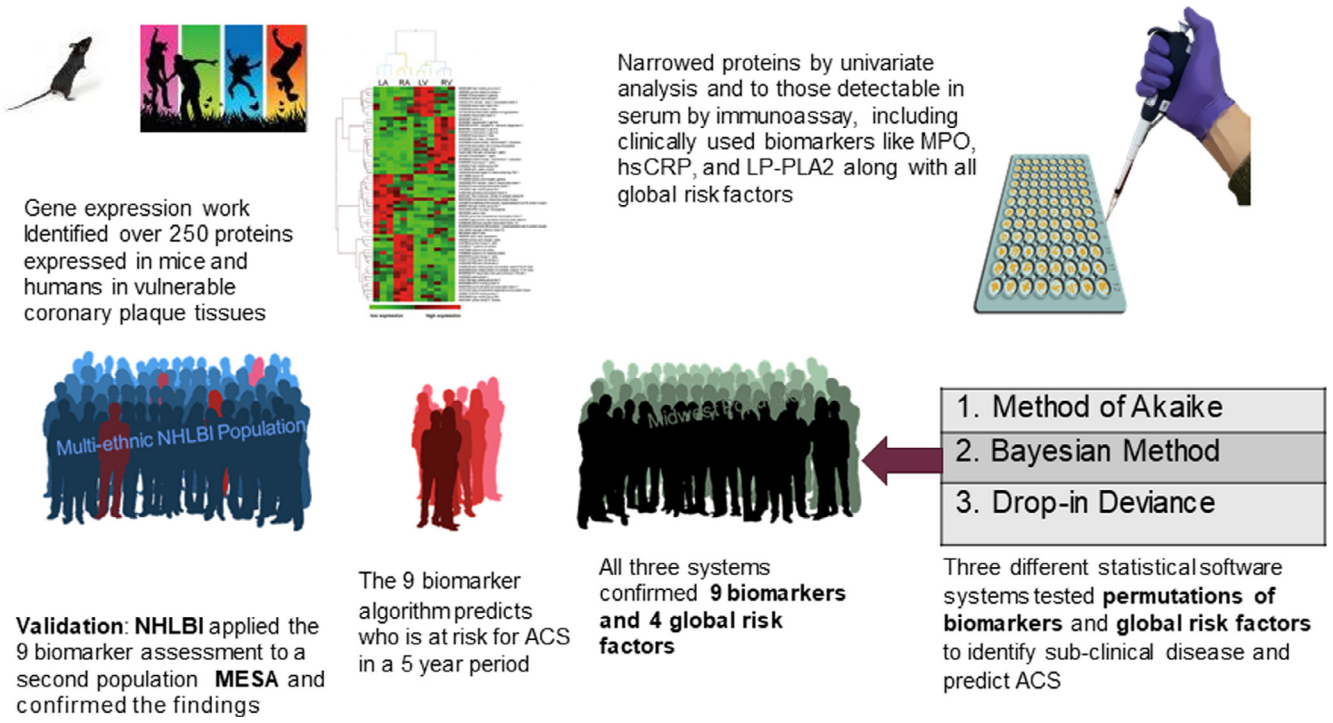

Figure 1. The process, development and validation of 9 serum biomarkers used in CADPA.
Abbreviations: ACS = acute coronary syndrome; hsCRP = high-sensitivity C-reactive protein; LP-PLA2 = lipoprotein-associated phospholipase A2; MESA = multiethnic study of atherosclerosis; MPO = myeloperoxidase; NHLBI = National Heart, Lung, and Blood Institute.

with triglycerides and obesity being particularly lower in included subjects.

Table 4 characterizes differences in those discordant versus nondiscordant between CADPA and the mFR global risk. Those discordant were older (mean age of 69.4 years vs 56.5 years, $p < 0.01$) and more likely men (63.6% vs 52.3%, $p < 0.01$). Hemoglobin A1c was also lower (5.7% vs 5.4%, $p < 0.01$) as was low-density lipoprotein-cholesterol (99.5 mg/dl vs 112.3 mg/dl, $p < 0.01$) in those discordant. Systolic blood pressure was higher in the

Table 2
Basic characteristics of the study cohort by CADPA Risk

Characteristics	CADPA risk			p value
	Low (0% to 3.49%)	Intermediate (3.5% to 7.49%)	High (>7.5%)	
Number of patients	694 (29.3%)	606 (26.7%)	1062 (45.0%)	
Age (years)	50.1 ± 10.6	61.0 ± 9.9	69.8 ± 10.2	<0.01
Male	303 (43.7%)	329 (54.3%)	711 (67.0%)	<0.01
Female	391 (56.3%)	277 (45.7%)	351 (33.1%)	<0.01
Body mass index (kg/m^2)	25.7 ± 4.5	26.7 ± 4.6	27.5 ± 4.6	<0.01
Hemoglobin A1c (%)	5.3 ± 0.5	5.4 ± 0.6	5.7 ± 0.9	<0.01
Total cholesterol (mg/dl)	201.1 ± 37.9	196.0 ± 43.5	183.7 ± 41.3	<0.01
Low-density lipoprotein-cholesterol (mg/dl)	113.4 ± 31.6	109.3 ± 34.2	101.8 ± 32.1	<0.01
High-density lipoprotein-cholesterol (mg/dl)	65.7 ± 16.8	63.5 ± 15.9	60.5 ± 14.8	<0.01
Triglycerides (mg/dl)	104.8 ± 70.4	108.5 ± 69.8	113.7 ± 72.9	0.03
Lipid-lowering medication, currently taking	139 (20.1%)	213 (35.32)%	568 (53.74%)	<0.01
Systolic blood pressure (mm Hg)	120.2 ± 15.7	125.8 ± 15.8	130.7 ± 17.3	<0.01
Diastolic blood pressure (mm Hg)	77.5 ± 10.0	78.0 ± 9.7	77.8 ± 10.5	0.63
Blood pressure medication, currently taking	130 (18.8%)	223 (36.9%)	594 (56.1%)	<0.01
Family history of cardiovascular disease	157 (22.7%)	228 (37.8%)	511 (48.3%)	<0.01
Obesity (body mass index ≥ 30 kg/m^2)	109 (15.7%)	121 (20.0%)	262 (24.8%)	<0.01
Smoker, current	34 (4.9%)	31 (5.12%)	66 (6.2%)	0.43
Presence of stress	229 (47.7%)	152 (40.5)%	229 (37.8%)	<0.01

Data are presented as mean ± standard deviation or number (percentage). CADPA risk is defined by percent risk of cardiovascular event in next 5 years. Stress is defined as subjective, self-reported stress above and beyond normal for the patient.

Table 3
Basic characteristics of the study cohort compared with excluded patients

Characteristics	Included cohort	Excluded cohort	p value
Number of Patients	2362 (37.5%)	3936 (62.5%)	
Age (years)	61.7 ± 13.2	59.3 ± 16.2	<0.01
Male sex	1343 (56.9%)	2191 (55.7%)	0.36
Body mass index (kg/m^2)	26.8 ± 4.6	27.6 ± 5.7	<0.01
Hemoglobin A1c (%)	7.0 ± 0.9	7.2 ± 1.34	<0.01
Total Cholesterol (mg/dl)	192.0 ± 41.6	196.7 ± 48.7	<0.01
LDL Cholesterol (mg/dl)	107.1 ± 32.9	105.9 ± 37.0	0.23
HDL Cholesterol (mg/dl)	62.8 ± 15.8	62.7 ± 17.9	0.78
Triglycerides (mg/dl)	109.7 ± 71.5	124.9 ± 130.0	<0.01
Lipid-lowering medication, currently taking	920 (39.1%)	1637 (44.2%)	<0.01
SBP (mm Hg)	126.4 ± 17.0	128.5 ± 18.9	<0.01
DBP (mm Hg)	77.8 ± 10.1	78.8 ± 11.6	<0.01
Blood pressure medication, currently taking	947 (40.2%)	1672 (45.1%)	<0.01
Family history of cardiovascular disease	896 (38.1%)	1537 (41.2%)	0.02
Obesity (body mass index ≥30 kg/m^2)	492 (20.9%)	1011 (27.1%)	<0.01
Smoker, current	131 (5.6%)	247 (6.6%)	0.10
Presence of stress	652 (41.5%)	933 (43.8%)	0.17

Data are presented as mean ± standard deviation or number (percentage). Stress is defined as subjective, self-reported stress above and beyond normal for the patient.

discordant group (mean 129.4 mm Hg vs 124.3 mm Hg, $p < 0.01$) and obesity less common (18.9% vs 23.8%, $p < 0.01$). Triglycerides and smoking status were not significantly different between the discordant and the nondiscordant groups, respectively.

Table 4
Comparison of patient characteristics between the discordant and nondiscordant groups

	Non discordant	Discordant	p value
	1403 (59.4%)	959 (40.6%)	
Age (years)	56.5 ± 12.3	69.4 ± 10.3	<0.01
Sex			
Male	733 (52.3%)	610 (63.6%)	<0.01
Female	670 (47.8%)	349 (36.4%)	<0.01
Body mass index (kg/m^2)	26.4 ± 4.6	27.4 ± 4.7	<0.01
Hemoglobin A1c (%)	5.4 ± 0.6	5.7 ± 0.8	<0.01
Total cholesterol (mg/dL)	199.1 ± 40.6	181.6 ± 40.8	<0.01
Low-density-lipoprotein cholesterol (mg/dL)	112.3 ± 32.9	99.5 ± 31.4	<0.01
High-density-lipoprotein cholesterol (mg/dL)	63.6 ± 16.5	61.6 ± 14.8	<0.01
Triglycerides (mg/dL)	110.3 ± 73.2	108.9 ± 68.8	0.65
Lipid-lowering medication, currently taking	389 (27.8)%	531 (55.6%)	<0.01
Systolic blood pressure (mm Hg)	124.3 ± 17.0	129.4 ± 16.6	<0.01
Diastolic blood pressure (mm Hg)	78.2 ± 10.1	77.2 ± 10.1	0.02
Blood pressure medication, currently taking	420 (30.0%)	527 (55.1%)	<0.01
Family history of cardiovascular disease	427 (30.5%)	469 (49.1%)	<0.01
Obesity (body mass index ±30 kg/m^2)	265 (18.92%)	227 (23.8%)	<0.01
Smoker, current	79 (5.6%)	52 (5.4%)	0.83
Presence of stress	416 (44.0%)	236 (37.8%)	0.02

Data are presented as mean ± standard deviation or number (percentage). CADPA risk is defined by percent risk of cardiovascular event in next 5 years. Stress is defined as subjective, self-reported stress above and beyond normal for the patient.

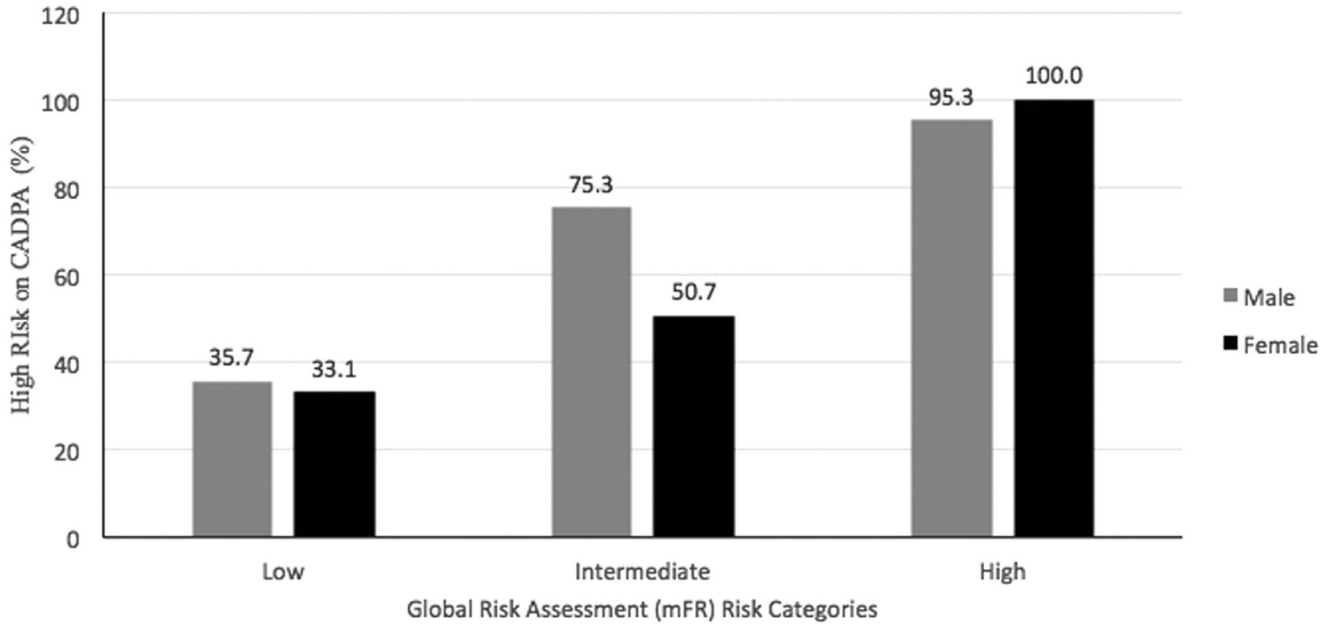

Figure 2. Percentage of patients with high risk (>7.5%) on CADPA compared between the genders in low (<3.5%), intermediate (3.5% to 7.49%), and high (>7.5%) global risk assessment (emFR) groups.

Table 5
Stepwise multiple logistic regression of biomarkers demonstrating modified Framingham/CADPA discordance

Step	Variable	Chi-squared	Odds ratio (95% confidence interval)	p value
1	Age*	518.85	1.12 (1.10−1.14)	<0.01
2	Interleukin-16*	215.90	2.59 (2.21−3.03)	<0.01
3	FasLigand*	112.60	0.50 (0.43−0.57)	<0.01
4	Hepatocyte growth factor*	98.22	1.72 (1.50−1.98)	<0.01
5	Soluble FAS*	76.94	2.19 (1.86−2.58)	<0.01
6	Cutaneous T cell-attracting chemokine*	86.92	0.46 (0.40−0.53)	<0.01
7	Eotaxin*	69.64	1.78 (1.56−2.03)	<0.01
8	Low-density-lipoprotein cholesterol	46.75	0.99 (0.99−0.99)	<0.01
9	Hemoglobin A1c*	9.64	1.28 (1.12−1.46)	<0.01
10	Systolic blood pressure	9.80	0.99 (0.98−1.00)	<0.01

* Variables found in the CADPA algorithm.Other variables in the model included monocyte chemotactic protein-3, triglycerides, body mass index, and high sensitivity c-reactive protein, but did not achieve significance of p <0.05. All odds ratios specified are per standard deviation for the variable indicated: 13.18 for age, 74.39 for interleukin-16, 34.0 for Fas Ligand, 159.73 for hepatocyte growth factor, 2285.71 for soluble FAS, 154.90 for cutaneous T cell-attracting chemokine, 74.43 for Eotaxin, 32.89 for low-density lipoprotein-cholesterol, 0.79 for hemoglobin A1c, 17.01 for systolic blood pressure.

Figure 2 further compares differences by gender in the low, intermediate, and high-risk mFR groups in proportion discordant by CADPA. A total of 34% of patients (36% of men and 33% of women) classified as low risk by mFR and 72% of patients (75% of men and 51% of women) classified as intermediate risk by mFR were classified as high risk by CADPA. 95% of men and 100% of women classified as high risk by mFR were also classified as high risk by CADPA.

The stepwise logistic regression analysis of the discordant subgroup is shown in Table 5. The 10 variables that were most predictive of discordance are, in order of confidence by Chi-squared value, age (1.12 [1.10 to 1.14]), interleukin-16 (2.59 [2.21 to 3.03]), Fas Ligand (0.50 [0.43 to 0.57]), hepatocyte growth factor (1.72 [1.50 to 1.98]), soluble FAS (2.19 [1.86 to 2.58]), cutaneous T cell-attracting chemokine (0.46 [0.40 to 0.53]), eotaxin (1.78 [1.56 to 2.03]), low density lipoprotein-cholesterol (0.99 [0.99 to 0.99]), hemoglobin A1c (1.28 [1.12 to 1.46]), and systolic blood pressure (0.99 [0.98 to 1.00]). All 10 of these variables achieved significant of p <0.05. Of these 10 variables, 8 were from the original CADPA algorithm: age, interleukin-16, Fas Ligand, hepatocyte growth factor, soluble FAS, cutaneous T cell-attracting chemokine, eotaxin, and hemoglobin A1c. The non-CADPA variables that predicted discordance include low-density lipoprotein-cholesterol and systolic blood pressure. The CADPA variable that entered the model but was excluded because it did not achieve significance of p <0.05 is monocyte chemotactic protein-3. High-density lipoprotein-cholesterol is a part of the CADPA test but was not predictive of discordance. Non-CADPA variables that entered the model but were excluded because they did not achieve significance included triglycerides, body mass index, and high sensitivity C-reactive protein.

Discussion

We show 34% of patients classified as low risk by mFR and 72% classified as intermediate risk were classified as high 5-year risk for ACS by CADPA, indicating traditional global risk assessment misclassifies many patients who are actually at high risk for ACS. Additionally, this study identified 10 patient factors that were most predictive of discordance.

Many biomarkers and risk factors have been identified over the years to provide accurate risk prediction.[6] The Pooled Cohort Risk Calculator also uses global risk factors, but often overestimates risk, especially in healthy populations.[8] These tools fail to identify many at discordantly high risk for ACS.

Previous studies have investigated single biomarkers for risk assessment, such as lipoprotein-associated phospholipase A2,[9] although prospective studies have questioned their individual role in the pathogenesis of atherosclerosis.[10,11] High-sensitivity C-reactive protein has also been a biomarker of interest,[12] but intraindividual[13] and ethnic[14] variability limits the ability of this single biomarker to consistently predict atherosclerosis.[15] The recent CANTOS study showed a significantly lower rate cardiovascular events by targeting interleukin-1β,[16] which affects several inflammatory markers, but using a single biomarker to predict risk has been challenging.

Individual biomarkers unlikely address processes that include multiple pathways in the formation of these unstable cardiac lesions.[6,7] Single biomarkers to predict coronary heart disease at best provide marginal improvement risk reclassification.[17,18] Multiple biomarker studies have been limited by only modest improvement in risk prediction[19] or in limited patient populations.[20]

Examining discordance in cardiovascular risk using biomarkers has primarily focused on comparing cholesterol with other lipid markers such as apolipoprotein B and low-density lipoprotein particle number,[21−23] but evaluation with the combination of clinical risk factors and a validated combination of cardiac biomarkers has not been, to our knowledge, studied to date.

CADPA measures endothelial injury and multiple inflammatory and repair pathways from serum biomarkers (hepatocyte growth factor, soluble FAS, Fas Ligand, eotaxin, cutaneous T cell-attracting chemokine, monocyte chemotactic protein-3, interleukin-16, hemoglobin A1c, and high-density lipoprotein-cholesterol) and global risk factors (age, gender, diabetes, and family history) to predict 5-year risk of ACS. CADPA has excellent risk-reclassification for coronary events, with a clinical net reclassification index of 42% (p <0.01) in MESA patients compared with mFR. A high-risk CADPA score previously identified 61% of ACS patients.[6]

In our cohort of 2,362 patients, men were more likely to have discordant risk: 64% of the discordant population was male and more men in both low and intermediate mFR risk were classified as high risk than women. Nearly all measured parameters differed between the discordant and nondiscordant patient groups except for lipid-lowering medication and smoking status. However, only 5% of patients were smokers in this population, requiring a significantly increased power to observe a difference between the discordant and nondiscordant

groups, and our patient population underestimated the national average smoking rate of 15.1% of all adults.[24]

We identified 10 variables that predict discordance, including 8 CADPA variables, suggesting that CADPA biomarkers capture most of the risk reclassification. This may be inherently because many of the biomarkers in CADPA measure the inflammatory and repair processes known to be critical in the pathophysiology of the disease. Interleukin-16, our greatest predictor of discordance, is a well-described immune cell chemoattractant for repair and proinflammatory processes like atherosclerotic cardiovascular disease. Fas Ligand and soluble FAS, involved in apoptosis and antiapoptosis pathways, respectively, and hepatocyte growth factor, involved in tissue remodeling, were also in the strongest predictors of discordance. Biopsies of unstable atherosclerotic coronary plaque have shown recruitment of immune cells such as T-cells, eosinophils, and macrophages.[5] Indeed, immune cell recruitment biomarkers like cutaneous T cell-attracting chemokine and eotaxin also predicted discordance. This suggests that CADPA is more accurately identifying high-risk patients through quantifying the activation of underlying pathophysiologic pathways involved in the formation of unstable coronary plaque.

Our study has several limitations. First, this was a cross-sectional study. A prospective study ideally focused on identifying those at risk of near-term ACS events would allow us to establish a temporal and causative relation between CADPA risk and cardiovascular events. This is partly mitigated by CADPA which was developed from 4 longitudinal patient cohorts predicting ACS in a 5-year timeframe (ADVANCE, Orentreich, PMRP-Marshfield, and MESA). Second, our analysis only used 38% of patients from our original cohort due to missing or implausible measures, and we did show some differences from those subjects not included, potentially limiting the generalizability of our results. Third, we did not have information on ethnicity to examine whether our results may differ by ethnicity. Fourth, the CADPA test measures 5-year risk of ACS and is compared with a modified Framingham measuring 5-year risk of cardiovascular disease; thus we did not directly compare equivalent end points. Last, we only compared CADPA with mFR and not other risk assessment tools such as the Pooled Cohort Risk Calculator, although CADPA outperforms Reynolds and a number of other risk models.[6]

In summary, this study characterizes a population at high risk for future acute coronary syndrome events based on the CADPA score, who are currently being classified as low or intermediate risk by global risk assessment. We also identify several key measures predicting this discordance. Although compelling, this current, real-world study will benefit from validation in larger, population-representative prospective studies to establish a temporal and causal relation between CADPA and cardiovascular disease events.

Disclosures

Dr. Harrington is an employee of GD Biosciences, Irvine, California. The other investigators have no relevant disclosures.

1. Zhang Z, Rautaharju P, Prineas R, Rodriguez C, Loehr L, Rosamond W, Kitzman D, Couper D, Soliman E. Race and sex differences in the incidence and prognostic significance of silent myocardial infarction in the atherosclerosis risk in communities (ARIC) study. *Circulation* 2016;133:2141–2148.
2. Kones R. Primary prevention of coronary heart disease: integration of new data, evolving views, revised goals, and role of rosuvastatin in management. A comprehensive survey. *Drug Des Dev Ther* 2011: 325.
3. Greenland P, Smith S, Grundy S. Improving coronary heart disease risk assessment in asymptomatic people: role of traditional risk factors and noninvasive cardiovascular tests. *Circulation* 2001;104:1863–1867.
4. Wexler L, Brundage B, Crouse J, Detrano R, Fuster V, Maddahi J, Rumberger J, Stanford W, White R, Taubert K. Coronary artery calcification: pathophysiology, epidemiology, imaging methods, and clinical implications: a statement for health professionals from the American Heart Association. *Circulation* 1996;94:1175–1192.
5. Falk E, Shah P, Fuster V. Coronary plaque disruption. *Circulation* 1995;92:657–671.
6. Cross D, McCarty C, Hytopoulos E, Beggs M, Nolan N, Harrington D, Hastie T, Tibshirani R, Tracy R, Psaty B, McClelland R, Tsao P, Quertermous T. Coronary risk assessment among intermediate risk patients using a clinical and biomarker based algorithm developed and validated in two population cohorts. *Curr Med Res Opin* 2012;28:1819–1830.
7. Ardigo D, Assimes T, Fortmann S, Go A, Hlatky M, Hytopoulos E, Iribarren C, Tsao P, Tabibiazar R, Quertermous T. Circulating chemokines accurately identify individuals with clinically significant atherosclerotic heart disease. *Phys Gen* 2007;31:402–409.
8. DeFilippis A, Young R, Carrubba C, McEvoy J, Budoff M, Blumenthal R, Kronmal R, McClelland R, Nasir K, Blaha M. An analysis of calibration and discrimination among multiple cardiovascular risk scores in a modern multiethnic cohort. *Ann Intern Med* 2015;162:266.
9. White H, Simes J, Stewart R, Blankenberg S, Barnes E, Marschner I, Thompson P, West M, Zeller T, Colquhoun D, Nestel P, Keech A, Sullivan D, Hunt D, Tonkin A. Changes in lipoprotein-associated phospholipase A2 activity predict coronary events and partly account for the treatment effect of pravastatin: results from the long-term intervention with pravastatin in ischemic disease study. *JAHA* 2013;2.e000360-e000360.
10. STABILITY Investigators, White HD, Held C, Stewart R, Tarka E, Brown R, Davies RY, Budaj A, Harrington RA, Steg PG, Ardissino D, Armstrong PW, Avezum A, Aylward PE, Bryce A, Chen H, Chen MF, Corbalan R, Dalby AJ, Danchin N, De Winter RJ, Denchev S, Diaz R, Elisaf M, Flather MD, Goudev AR, Granger CB, Grinfeld L, Hochman JS, Husted S, Kim HS, Koenig W, Linhart A, Lonn E, López-Sendón J, Manolis AJ, Mohler ER 3rd, Nicolau JC, Pais P, Parkhomenko A, Pedersen TR, Pella D, Ramos-Corrales MA, Ruda M, Sereg M, Siddique S, Sinnaeve P, Smith P, Sritara P, Swart HP, Sy RG, Teramoto T, Tse HF, Watson D, Weaver WD, Weiss R, Viigimaa M, Vinereanu D, Zhu J, Cannon CP, Wallentin L. Darapladib for preventing ischemic events in stable coronary heart disease. *New Engl J Med* 2014;370:1702–1711.
11. O'Donoghue M, Braunwald E, White H, Steen D, Lukas M, Tarka E, Steg P, Hochman J, Bode C, Maggioni A, Im K, Shannon J, Davies R, Murphy S, Crugnale S, Wiviott S, Bonaca M, Watson D, Weaver W, Serruys P, Cannon C. Effect of darapladib on major coronary events after an acute coronary syndrome. *JAMA* 2014;312:1006.
12. Musunuru K, Kral B, Blumenthal R, Fuster V, Campbell C, Gluckman T, Lange R, Topol E, Willerson J, Desai M, Davidson M, Mora S. The use of high-sensitivity assays for C-reactive protein in clinical practice. *Nat Clin Prac Cardiovas Med* 2008;5:621–635.
13. deGoma E, French B, Dunbar R, Allison M, Mohler E, Budoff M. Intraindividual variability of C-reactive protein: the multi-ethnic study of atherosclerosis. *Atherosclerosis* 2012;224:274–279.
14. Woloshin S, Schwartz L. Distribution of C-reactive protein values in the United States. *New Engl J Med* 2005;352:1611–1613.
15. Yousuf O, Mohanty B, Martin S, Joshi P, Blaha M, Nasir K, Blumenthal R, Budoff M. High-sensitivity C-reactive protein and cardiovascular disease. *J Am Coll Cardiol* 2013;62:397–408.
16. Ridker P, Everett B, Thuren T, MacFadyen J, Chang W, Ballantyne C, Fonseca F, Nicolau J, Koenig W, Anker S, Kastelein J, Cornel J, Pais P, Pella D, Genest J, Cifkova R, Lorenzatti A, Forster T, Kobalava Z, Vida-Simiti L, Flather M, Shimokawa H, Ogawa H, Dellborg M, Rossi P,

Troquay R, Libby P, Glynn R. Antiinflammatory therapy with canakinumab for atherosclerotic disease. *New Engl J Med* 2017;377:1119–1131.
17. Wilson P, Pencina M, Jacques P, Selhub J, D'Agostino R, O'Donnell C. C-reactive protein and reclassification of cardiovascular risk in the framingham heart study. *Circ Cardiovas Qual Outcomes* 2008;1:92–97.
18. The Lp-PLA2 Studies Collaboration. Lipoprotein-associated phospholipase A2 and risk of coronary disease, stroke, and mortality: collaborative analysis of 32 prospective studies. *The Lancet* 2010;375:1536–1544.
19. Wang T, Gona P, Larson M, Tofler G, Levy D, Newton-Cheh C, Jacques P, Rifai N, Selhub J, Robins S, Benjamin E, D'Agostino R, Vasan R. Multiple biomarkers for the prediction of first major cardiovascular events and death. *New Engl J Med* 2006;355:2631–2639.
20. Zethelius B, Berglund L, Sundström J, Ingelsson E, Basu S, Larsson A, Venge P, Ärnlöv J. Use of multiple biomarkers to improve the prediction of death from cardiovascular causes. *New Engl J Med* 2008;358:2107–2116.
21. Mora S, Buring J, Ridker P. Discordance of low-density lipoprotein (LDL) cholesterol with alternative LDL-related measures and future coronary events. *Circulation* 2013;129:553–561.
22. Costello B, Silverman E, Doukky R, Braun L, Aggarwal N, Deng Y, Li Y, Lundberg G, Williams K, Volgman A. Lipoprotein(a) and increased cardiovascular risk in women. *Clin Cardio* 2016;39:96–102.
23. Nordestgaard B, Tybjærg-Hansen A. Genetic determinants of LDL, lipoprotein(a), triglyceride-rich lipoproteins and HDL: concordance and discordance with cardiovascular disease risk. *Curr Opin Lipid* 2011;22:113–122.
24. Benjamin E, Virani S, Callaway C, Chamberlain A, Chang A, Cheng S, Chiuve S, Cushman M, Delling F, Deo R, de Ferranti S, Ferguson J, Fornage M, Gillespie C, Isasi C, Jiménez M, Jordan L, Judd S, Lackland D, Lichtman J, Lisabeth L, Liu S, Longenecker C, Lutsey P, Mackey J, Matchar D, Matsushita K, Mussolino M, Nasir K, O'Flaherty M, Palaniappan L, Pandey A, Pandey D, Reeves M, Ritchey M, Rodriguez C, Roth G, Rosamond W, Sampson U, Satou G, Shah S, Spartano N, Tirschwell D, Tsao C, Voeks J, Willey J, Wilkins J, Wu J, Alger H, Wong S, Muntner P. Heart disease and stroke statistics—2018 update: a report from the American Heart Association. *Circulation* 2018;137:e67–e492.